Featured Correspondence

Effects of glycoprotein IIb/IIIa blockers

To the Editor: The meta-analysis by Hernandez *et al*[1] showed that the reduction of death or non-fatal myocardial infarction with IIb/IIIa inhibitors in patients with an acute coronary syndrome (ACS) was independent of patient age. The trials included were performed before widespread administration of clopidogrel in ACS.

Clopidogrel has been shown to be beneficial in ACS; its administration is a class I recommendation.[2] Glycoprotein IIb/IIIa inhibition is a class I recommendation only in patients with planned percutaneous coronary intervention (PCI) in the absence of clopidogrel, but is a class IIa recommendation in patients already treated with clopidogrel.[2]

An analysis of the National Registry of Myocardial Infarction-4 suggested that routinely giving a glycoprotein IIb/IIIa inhibitor to patients with a non-ST-elevation ACS treated with clopidogrel might not be justified, especially if PCI were not performed.[3] This may be particularly true in elderly patients, since virtually all studies indicate that elderly patients are more likely to bleed than younger patients; bleeding has been shown to be an independent predictor of mortality in both ACS and PCI patients.[4]

An analysis of the ISAR-REACT 2 trial showed that abciximab did not reduce the 30-day incidence of death or any other component of major adverse cardiac events in older patients with a non-ST-elevation ACS treated with clopidogrel; in fact, it seemed to be harmful.[5] We are currently analysing the relationship between age and outcome in three other ISAR studies.

In conclusion, while we applaud the excellent analysis of the authors, we caution that the results of their meta-analysis may not be generalisable to all patients with ACS, particularly the elderly pretreated with clopidogrel.

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Competing interests: None declared.

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The authors' reply: We thank Drs Kalyanasundaram, Kastrati and Berger for their interesting comments about our article.

Patients included in our subgroup meta-analysis were not routinely scheduled for an early coronary revascularisation, so our results are not directly comparable with the ISAR trials. Patients did not receive clopidogrel as background medication at the time of admission, but almost all received dual antiplatelet treatment at the time of percutaneous coronary intervention (PCI). We agree that clopidogrel is recommended in patients with non-ST segment elevation ACS (NSTEACS) whether or not an invasive approach is planned.[1] The concern, however, is the timing of clopidogrel administration, which continues to be debated, with many cardiologists electing to withhold clopidogrel until angiography because of concerns about bleeding with bypass surgery.[2] This approach is consistent with the treatment strategy applied in the trials included in our meta-analysis.

We agree that troponin-negative patients with moderate-to-high risk NSTEACS seem to have less benefit than troponin-positive patients, as we have shown in a previous post hoc subgroup analysis from our dataset.[3] We acknowledge, however, that the analysis was a retrospective subgroup analysis with poor power.

We appreciate the major contribution that the ISAR trials have made to clinical practice, but they differ significantly from trials included in our meta-analysis. It is critical to avoid direct extrapolation from trials testing adjunctive treatments for PCI (as in the ISAR trials) to trials evaluating strategies of initial medical treatment with PCI performed if needed some time later (in many cases several days later). It is also particularly important to avoid scientifically inappropriate subgroup analyses, in which the subgroup is formed at variable times *after* the treatment allocation.[4]

In the patchwork of evidence from clinical trials several strategies have emerged as viable. Our meta-analysis was meant to provide a context for clinicians choosing a strategy of initial medical treatment followed by consideration of angiography at a later date with deferred initiation of clopidogrel. We agree that our results should not be directly extrapolated beyond that point. In general, our analysis in the severe subset of our patients with NSTEACS shows a similar trend to the age analysis of the ISAR-REACT 2 trial. We look forward to seeing the results of the analysis of the relation between age and outcomes in the four ISAR trials. Furthermore, the continuing EARLY-ACS trial has enrolled over 6000 patients in a trial directly testing the role of eptifibatide in the setting of ''upstream'' clopidogrel use, with an emphasis on enrolment of an elderly population.[5]

We welcome further interchange and appropriate contrasts of clinical trials carried out in different circumstances in different populations.

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Competing interests: None declared.

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